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Medical Progress

Paraneoplastic Syndromes

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Neoplasms can produce a variety of remote effects on the host; these are referred to as paraneoplastic syndromes. The syndromes may affect any of the systems of the body, may precede or follow the diagnosis of the underlying neoplasm, and may or may not parallel the course of the neoplasm in severity. The diagnosis of and therapy for these syndromes can be challenging to a physician, but successful therapy may bring about worthwhile relief for the patient. In addition, the syndromes and the substances that cause them are sometimes useful in diagnosing and in following the course of certain neoplasms. Perhaps of greater importance, study of these remote effects of neoplasia may shed light on the nature of the neoplastic process itself.

THE RECOGNITION that neoplasms can produce remote effects on the host is not recent. It is over a century since Trousseau described recurrent thrombophlebitis in association with his own gastric carcinoma. However, over the past decade there has been increasing interest in these phenomena. Initially, these remote effects of neoplasia were thought to be uncommon, as indeed some are; others, however, are now known to be of frequent occurrence. The term *paraneoplastic syndromes* is used here as synonymous with remote effects of neoplasia. In some instances the syndrome has been ascribed to production of a hormone by the tumor; in other instances the mechanism remains obscure.

These syndromes are important for several reasons. First, they occasionally aid in the early diagnosis of the neoplasm. Second, the syndromes have aided in the discovery that many (and perhaps most) neoplasms produce hormones or other substances that can be used as tumor markers.[1] These markers are of increasing use in early diagnosis and in following the course of neoplasms during therapy. Third, the syndromes often provide the opportunity for meaningful symptomatic relief, whether or not the neoplasm itself can be successfully treated. Fourth, and perhaps most important, the syndromes have heuristic value. If we understood the precise mechanisms whereby neoplasms produce these remote effects, we would be closer to understanding the nature of the neoplastic process itself.

For further data and references, the reader is referred to the monograph by Waldenstrom[2] and that edited by Hall,[3] as well as recent reviews.[1,4-9]

Endocrine Disorders

Perhaps the most secure method of documenting the production of a hormone by a neoplasm is to show such production in a cell culture. Almost equal in certainty is the finding of an arteriovenous increase in concentration of the hormone in vessels supplying the neoplasm. Immunochemical or histochemical localization of the hormone in the neoplasm is useful but does not prove

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
APUD = amine precursor uptake and decarboxylation
NSILA = nonsuppressible insulin-like activity
PML = progressive multifocal leukoencephalopathy
SIADH = inappropriate secretion of antidiuretic hormone

production as opposed to storage. A greater concentration of the hormone in the neoplasm than in the adjacent tissue helps to rule out the latter as the source of the hormone. Less certain still is the finding of an elevated level of circulating hormone in the presence of a neoplasm derived from a tissue that does not normally produce that hormone; here, there may be a coexisting adenoma of the gland which normally produces the hormone. Subsidence of the syndrome and of the elevated circulating hormone level following resection of a neoplasm is frequently the only available evidence of hormone production by the neoplasm, but these findings do not rule out production by adjacent tissue removed with the neoplasm. Recurrence of the syndrome and of the elevated hormone level in association with distant metastases provides better evidence.

These criteria should be kept in mind when one reads reports of the putative paraneoplastic syndromes. Recent reviews have examined the degree to which the criteria have been met in reports of hormone production by neoplasms.[2,5-9] In general, bioassay of hormones is relatively insensitive but correlates well with clinical effects. Immunoassay is more sensitive but may measure biologically inactive prohormones or hormone fragments as well as active hormones, all of which may be produced by neoplasms.[4] Among the prohormones only progastrin has noteworthy biologic activity.[4] The term ectopic is used to describe production of a substance by a neoplasm derived from a tissue which is not believed to produce that substance under normal conditions.

*Cushing Syndrome**

In 1928, before Cushing's description of the syndrome that bears his name, Brown reported weakness, hyperpigmentation, hirsutism, truncal obesity, edema, hypertension and hyperglycemia in a woman with small cell carcinoma of the lung. Bilateral adrenocortical hyperplasia was noted at autopsy. Since then more than 200 cases have been reported of hypercorticism associated with nonadrenal and nonpituitary neoplasms. Most have been small cell carcinomas of the lung,[1-8,10-12] with occasional cases of lung cancer of other cell types[13] as well as bronchial carcinoids.[11] In addition, there have been scattered cases of malignant epithelial thymoma, islet cell carcinoma, small cell carcinoma of other sites, carcinoids of other sites, and carcinomas of the larynx[11] and salivary glands, medullary thyroid carcinoma,[2] ovarian carcinoma,[2] pheochromocytoma,[6] and possibly other neoplasms. Most of these neoplasms are of the amine precursor uptake and decarboxylation (APUD) series (see below).[2,6] It has been estimated that 15 percent of patients with Cushing syndrome have nonadrenal and nonpituitary neoplasms.

The clinical features[2,4,5,8,11] of hypercorticism associated with nonadrenal and nonpituitary neoplasms usually do not include a cushingoid fat distribution, probably because of the brevity of survival and the cachexia which accompanies most cases. Hyperpigmentation is seen in 23 percent, hypertension in 36 percent, edema in 30 percent, fasting hyperglycemia in 38 percent, and impaired glucose tolerance in 93 percent of cases.[11] A hypokalemic alkalosis is present in 72 percent and can be of life-threatening severity.[11] Laboratory findings[2,4,5,8,11] include substantially elevated plasma cortisol levels, as well as elevation of urinary 17-hydroxycorticoid and (in 33 percent) 17-ketosteroid excretion. The latter may be associated with masculinization in female patients. Diurnal variation in steroid production is absent. Hypernatremia is an occasional finding.

The syndrome is due to production of adrenocorticotropic hormone (ACTH)[4] by the neoplasm which causes adrenal cortical hyperplasia with excessive production of glucocorticoids, mineralocorticoids and androgens. Plasma ACTH levels are usually higher than are seen with overproduction of ACTH by the pituitary.[4] Selective venous sampling can confirm the site of ACTH production but is rarely necessary.[14] In addition to ACTH, most and perhaps all of these neoplasms also produce "big" or pro-ACTH,[4,15] which has little biologic activity. An uncertain percent of these neoplasms also produce corticotropin-releasing hormone (CRH), which stimulates the pituitary to produce more ACTH.[11,16] It is possible that these CRH-producing neoplasms, particularly bronchial car-

*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

cinoids, include the rare cases in which dexamethasone will partially suppress[4] or metyrapone will increase 17-hydroxycorticoid excretion. In most patients, neither dexamethasone nor metyrapone will affect steroid excretion.[11] The hyperpigmentation has been ascribed to ACTH and to β-melanocyte-stimulating hormone (β-MSH), although β-MSH may be an artifact; the compound measured by immunoassay is probably β-lipotropin.[1,4] Nonetheless, hyperpigmentation is important clinically, in that its presence in association with hypercorticism almost always indicates that the syndrome is due to ACTH production (by a pituitary or other neoplasm) and not to a primary adrenal disorder.

Removal of the tumor is possible in only about 10 percent of patients. Hence, palliative therapy is important. Successful radiotherapy or chemotherapy of the neoplasm can alleviate the hormonal syndrome. In addition, therapy directed at decreasing the production of glucocorticoids and mineralocorticoids can bring considerable symptomatic relief.[1,2,4,5,8,11] Mitotane is toxic to the adrenal cortex. Aminoglutethimide inhibits the first step in the production of all corticoids. Metyrapone inhibits 11-β-hydroxylase, thus blocking the production of cortisol, corticosterone and aldosterone. Hence, metyrapone can cause a decline in levels of those steroids which cause symptoms, although in most cases the total steroid excretion remains the same. Spironolactone can block the actions of mineralocorticoids, but large doses may be required. Therapy for hypokalemia, hypertension or diabetes may be necessary as well. Bilateral adrenalectomy is rarely indicated; as is the case with the antihormonal agents, the syndrome will be relieved with the exception of the hyperpigmentation.

Hypoglycemia

One must be careful to define the normal range for blood glucose; in normal women it may fall to 35 mg per dl after a 72-hour fast. More than 200 cases of fasting hypoglycemia have been reported with nonislet cell neoplasms.[17,18] About 42 percent of these have been of mesenchymal origin, including fibrosarcomas, other sarcomas, benign fibromas and mesotheliomas. Another 22 percent were liver cell carcinomas, with occasional examples of adrenal cortical carcinoma, lymphoma, gastrointestinal carcinoma and other carcinomas. Most of the neoplasms were large, ranging from 800 grams to several kilograms, and more than 80 percent were abdominal. Other causes of fasting hypoglycemia include starvation, severe liver disease, and insufficiency of anterior pituitary, thyroid or adrenal cortical function. Symptoms of hypoglycemia include central nervous system abnormalities ranging from confusion to coma, seizures and focal defects. Adrenergic symptoms include sweating, tremor and palpitations, but they tend to be related to the rapidity of the fall in serum glucose rather than to its depth.

It was first supposed that the neoplasms produced insulin or proinsulin, but with a few possible exceptions,[4] this has not been substantiated. In this connection, a source of confusion has been the rare islet cell carcinoma with metastases resembling a spindle cell neoplasm. Because of the large size of these neoplasms, it was proposed that excessive consumption of glucose was the mechanism responsible for hypoglycemia. In rare cases it has been possible to show an arteriovenous glucose difference in vessels supplying the tumor or excessive glucose consumption in vitro.[17] The most likely mechanism in most cases is the production by the tumor of a substance (or substances) with insulin-like activity on bioassay but which is not identical to insulin on immunoassay. This activity is referred to as nonsuppressible insulin-like activity (NSILA) because it is not suppressed by anti-insulin antibodies.[19,20] This NSILA is not abnormal per se and makes up most of the circulating insulin-like activity on bioassay in normal persons. However, its persistence in the circulation at high levels in the presence of hypoglycemia is abnormal. The most readily available test to distinguish islet cell from nonislet cell neoplasms which produce hypoglycemia is to assay for the C-peptide, which is present in proinsulin and is produced by virtually all islet cell neoplasms; it is absent from NSILA. It is also absent in cases of surreptitious insulin injection, but this would be an unlikely consideration in a cancer patient. The NSILA has been tentatively identified with somatomedins; these low molecular weight peptides are produced in the liver and possess both growth-promoting and insulin-like activity.[19,20] Their relation to neoplastic growth is unknown. A final possibility in the causation of hypoglycemia is defective hepatic glycogenolysis. Rare case reports appear to document decreased phosphorylase activity in some liver cell carcinomas and in the adjacent liver tissue, resulting in abundant hepatic glycogen despite severe hypoglycemia. It is possible that this acquired glycogen

storage disease occurs in more cases of liver cell carcinoma than is now apparent.

Therapy includes removal of as much of the tumor as possible, and therapy with irradiation or antineoplastic agents may alleviate the hypoglycemia. Chemotherapy for islet cell neoplasms sometimes results in a transient worsening of the hypoglycemia as insulin is released from dying neoplastic cells. However, this transient aggravation of hypoglycemia is rare in chemotherapy for nonislet cell neoplasms, although such a phenomenon did occur in one case of Hodgkin disease.[17] If antineoplastic therapy is unsuccessful, symptomatic therapy[17,18] may help to prevent severe hypoglycemia. One may employ frequent feedings, glucagon, diazoxide or perhaps glucocorticoids. Continuous glucose infusions are necessary in severe cases. Mithramycin has relieved hypoglycemia in islet cell carcinoma; it would be interesting to try this agent in treating other neoplasms which produce hypoglycemia.

Spurious hypoglycemia may occur in leukemias with high counts of circulating leukocytes. If the blood is drawn into a plain tube and the serum not separated promptly, the cells continue to metabolize glucose. The problem is obviated by separating the serum immediately, or by ensuring that sufficient fluoride is present in the tube to stop metabolism.

Hyperglycemia

Hyperglycemia[21] is not often considered as a concomitant of neoplasia. Starvation, impairment of pancreatic or hepatic function, coexisting diabetes mellitus, or exogenous or endogenous glucocorticoids can cause impairment of glucose tolerance.[5] Such impairment has also been reported in association with glucagon-producing islet cell neoplasms and an enteroglucagon-producing renal carcinoma. Hyperglycemia has been reported in association with a somatostatin-containing islet cell neoplasm, although circulating glucagon levels were also elevated. In addition, impairment of glucose tolerance has been reported in some patients with osteosarcoma.[22] In these patients, a glucose load resulted in an accentuated response of both growth hormone and insulin. This interrelationship deserves further study. Growth hormone might be of some pathogenetic significance in osteosarcoma; the peak incidence occurs during rapid skeletal growth, and patients tend to be taller than average. Hyperglycemia has not been reported in association with prostaglandin-containing neoplasms; however, such an association might be suspected, based on the observation that prostaglandins blunt the insulin response to a carbohydrate load.

Hypercalcemia

Hypercalcemia occurs in about 0.3 percent of patients in a general hospital; of these, about 20 percent have cancer and only 5 percent have hyperparathyroidism. In 10 percent to 20 percent of patients with cancer, hypercalcemia develops at some time;[4] usually it is due to "direct" lysis of bone by osseous metastases. This mechanism is incompletely understood; osteoclast-activating factor, prostaglandins, low pH, and perhaps pressure may each play a role. In addition, hypercalcemia has been reported in hundreds of patients without detectable bony metastases, although it is possible that neither radiographs, radionuclide scans, nor routine autopsies are uniformly effective in detecting bony metastases.

Elevated levels of parathyroid hormone (parathormone) have been reported in a variety of neoplasms.[23-27] The most common of these neoplasms is squamous carcinoma of the lung, with adenocarcinoma and large cell carcinoma being less common and small cell carcinoma rare.[26] Squamous carcinomas of the head and neck region are also relatively common.[25] A wide variety of neoplasms, including mainly carcinomas but also occasional lymphomas and leukemias, has been associated with elevated parathormone levels. In some cases it was possible to establish that the neoplasm produced parathormone in vitro.[27,28] In other cases selective venous sampling disclosed that the source of the parathormone was the parathyroid glands and not the suspected ectopic source. It should be recalled that prior irradiation of the neck can give rise to parathyroid neoplasms. The frequency with which ectopic production of parathormone is a feature of neoplasms has been estimated at high[23] and low[24] levels. Parathyroid "hyperplasia" has been said to be a frequent finding at autopsy of patients with cancer. However, it is defined as a reduction in parathyroid fat; it may represent glandular hyperplasia or simply loss of fat due to cachexia. Further data should clarify the question of how often the hypercalcemia in patients with neoplasms is caused by ectopic production of parathormone. One source of confusion is that some neoplasms produce proparathormone[27] or the inactive carboxy-terminal fragment of parathormone, both

of which may be detected in an immunoassay for parathormone.

Elevated levels of prostaglandins, particularly prostaglandin-E2, have been reported in association with a variety of neoplasms, mainly carcinomas.[27,29-32] Because prostaglandins are widely distributed in normal tissues, it is doubtful that the term ectopic should be used in this connection. Increased concentrations of prostaglandin-E2 and cyclic AMP (adenosine-5-monophosphate) have been found in neoplastic cells;[31] production by these cells is likely.[32] That prostaglandins play a role in the hypercalcemia associated with neoplasms is supported by the relief of hypercalcemia in some patients with the use of the prostaglandin antagonists acetylsalicylic acid and indomethacin.[29,30] Osteoclast-activating factor has been reported in myeloma[33] and similar bone-resorbing activity in acute lymphocytic leukemia[34] as well as in phytohemagglutinin-stimulated normal lymphocytes.[4] As is the case with prostaglandins,[32] it is as yet unclear how often these bone-resorbing factors produce hypercalcemia as a remote effect as opposed to promoting bone lysis in situ. Non-vitamin D sterols have been reported in breast cancer, but have not been confirmed. For uncertain reasons some vasoactive-intestinal-polypeptide-producing neoplasms have been associated with hypercalcemia.[27]

Additional causes of hypercalcemia in patients with breast cancer are estrogen, androgen, progestin or antiestrogen therapy.[27] Whatever the underlying cause, hypercalcemia can be aggravated by immobilization, dehydration, thiazide administration, adrenal insufficiency and hyperthyroidism.[27] Hypercalcemia frequently accompanies paraproteinemia in myeloma and related disorders. Usually this represents a potentially dangerous elevation of ionized calcium. Occasionally, however, the excess serum calcium is entirely bound to the paraprotein, and the ionized calcium level is normal.[35] Therapy for hypercalcemia has been reviewed.[27,35-37] Of interest are the effects of dactinomycin and mithramycin in blocking DNA-dependent RNA synthesis and blocking the effects of parathormone and vitamin D on bone,[38] as well as the effect of glucocorticoids in blocking the action of osteoclast-activating factor[39] and the synthesis of prostaglandins.[40]

Hypocalcemia and Osteomalacia

Hemangiomas[41] and, rarely, other mesenchymal neoplasms may be associated with osteomalacia, hypophosphatemia, bone pain, muscle weakness and renal phosphate wasting. Serum calcium is usually normal, but in one case this may have been due to a coexisting parathyroid adenoma. The syndrome was improved by therapy with vitamin D and phosphate and resolved following removal of the neoplasm. The neoplasm apparently produces a substance which affects the tubular resorption of phosphate.[41] Hypocalcemia is an infrequent concomitant of neoplasia.[37] Medullary carcinoma of the thyroid, small cell carcinoma of the lung, and, occasionally, other neoplasms can produce calcitonin,[42] but hypocalcemia is rare in these patients. Calcium uptake into osteoblastic metastases is an infrequent cause of hypocalcemia.[43] Additional causes include malabsorption, renal insufficiency, hypomagnesemia, hyperphosphatemia, anticancer agents, and destruction of the parathyroid glands by surgical procedure or cancer.[37]

Inappropriate Secretion of Antidiuretic Hormone

Inappropriate secretion of antidiuretic hormone (SIADH) has been reported in over 100 patients with neoplasms.[44-46] In one series of 86 patients with SIADH, 20 had cancer; of these, 14 had lung cancer,[45] usually small cell carinomas. Occasional reports describe the syndrome in patients with neoplasms of the digestive system[45,46] and, in rare cases, with other neoplasms including lymphoma.[4,45] Strict criteria for the diagnosis of SIADH should be kept in mind.[44,45] The syndrome is also present in patients with a variety of benign conditions of the lungs and nervous system.[45] In view of this, plus the fact that the most common neoplastic cause is lung cancer, a question arises as to whether the vasopressin is produced in the neoplasm or as a response to the neoplasm. In some cases,[2,6] production by the tumor has been shown. Additional causes of SIADH includes vincristine, which appears to increase the level of antidiuretic hormone as a neurotoxic effect,[45] and high-dose cyclophosphamide, which appears to exert a direct but transitory effect on the kidney through its metabolites.[45] Other drugs may have similar effects.[44] The symptoms of hyponatremia include confusion and seizures. The therapy for SIADH has been reviewed[44,45] and includes fluid restriction and demeclocycline, which blocks the renal effects of vasopressin.[47] Aggravation of SIADH should be avoided by close monitoring of serum

sodium levels when patients with cancer receive intravenous infusions.

Diabetes Insipidus

Diabetes insipidus can result from destruction of the posterior pituitary by a neoplasm.[45] The condition occurs in 0.95 percent of patients with breast cancer. Metastatic breast cancer is the most frequent cause of diabetes insipidus in women over the age of 60,[45] while lung cancer is the most frequent cause of pituitary metastasis in men. Of patients with metastasis to the pituitary, 7 percent have diabetes insipidus and 1 percent have panhypopituitarism. Of course, these represent direct effects of a neoplasm and are included for completeness. Nephrogenic diabetes insipidus in patients with cancer can result from hypercalcemia, hypokalemic nephropathy, renal amyloidosis and sudden relief of urinary obstruction.[45]

Carcinoid Syndrome

The carcinoid syndrome has been reported in rare cases of noncarcinoid neoplasms, including adenocarcinoma of the pancreas, islet cell neoplasms, small cell carcinoma of the lung, medullary carcinoma of the thyroid, and carcinoma of unknown primary site.[48] Most of these neoplasms originated from cells of the APUD series.

Gynecomastia

Gynecomastia is a frequent finding in nonseminomatous carcinomas of the testis[49] and a rare finding in liver cell[50] and renal cell carcinomas, large cell and other lung carcinomas, and other neoplasms. A careful study of patients with testicular cancer[49] showed that the β subunit of chorionic gonadotropin, prolactin, estrone, and estradiol in various permutations were all correlated with gynecomastia, but each alone could be increased in the absence of gynecomastia or could be normal in its presence. Neoplastic cells[51] and the normal placenta[52] can aromatize C19 androgenic precursors into estrogens. Cirrhosis and drugs such as digitalis, estrogens, phenothiazines and spironolactone can also produce gynecomastia. In addition, gynecomastia has been observed in adolescent males and, rarely, in men treated with antineoplastic agents; presumably this is a result of damage to the androgen-producing cells. A related syndrome is precocious puberty, which has been reported in young boys with hepatic neoplasms which produced chorionic gonadotropin.[53] There is evidence that neoplasms can produce a chorionic gonadotropin lacking in carbohydrate; this compound may be cleared from the blood too rapidly to be detected or to produce biologic effects.[4] This fact may explain why gonadotropin production by neoplasms may be much more frequent than had been appreciated.[1,4]

Hyperthyroidism

Hyperthyroidism is a very rare concomitant of nonthyroid neoplasms.[54,55] Most of these patients had a hydatidiform mole or choriocarcinoma, with isolated instances of nonseminomatous testicular carcinoma. Other patients may have laboratory evidence of thyroid hyperfunction without clinical signs.[2] The syndrome appears to be caused by the thyroid-stimulating effects of chorionic gonadotropin rather than by a separate hormone.[55] With one possible exception,[2] there have been no documented examples of ectopic production of thyrotropin.

Hypertension

Besides its well-known association with pheochromocytoma, neuroblastoma and aldosteronoma, hypertension has been reported in association with renal neoplasms including hemangiopericytoma, Wilms tumor, and renal cell carcinoma.[56] The hemangiopericytomas appear to be derived from juxtaglomerular cells, which produce renin under normal conditions. Hence, they may be regarded as endocrine tumors; the elevated renin levels they produce are not of ectopic origin. The situation with Wilms tumor and renal cell carcinoma is less clear. High levels of renin in plasma have been reported with these tumors; the renin levels and blood pressure may decrease following nephrectomy.[56] In these cases, it seems possible that the renin was produced by the adjacent, compressed renal tissue. However, there are isolated reports of recurrent hypertension with the appearance of distant metastases of renal cell carcinoma.[56] Here it seems likely that the metastases produced renin. There is a report of a renin-containing carcinoma of the lung associated with hypokalemia and hypertension.[57]

Hematologic Disorders

Polycythemia

The upper limit (mean +2 SD) of red blood cell mass as measured with chromium 51 at sea level ranges from 29.6 to 30.6 ml per kg of body weight in women and from 33.9 to 36.5 in men.

Polycythemia, a level above these ranges, has been reported in over 300 patients with neoplasms.[56,58] Most of the these have been renal (renal cell carcinoma or Wilms tumor), with liver cell carcinoma the next in frequency.[56,58] Polycythemia has also been associated with cerebellar hemangioblastoma and with occasional examples of other neoplasms, including leiomyoma of the uterus and others.[56,58] In addition, polycythemia has been associated with such nonneoplastic renal lesions as cystic disease and hydronephrosis. Unlike polycythemia vera, the polycythemia associated with neoplasms is usually not accompanied by leukocytosis, basophilia, eosinophilia or thrombocytosis. Other causes of polycythemia include cardiopulmonary disease, abnormal hemoglobins, and endogenous or exogenous androgens.[56,58] Alveolar hypoventilation should be ruled out in the presence of a brain tumor and carboxyhemoglobinemia in a smoker. Between 1 percent and 5 percent of patients with renal neoplasms have polycythemia, and a similar proportion of patients with polycythemia have a renal neoplasm.[56,58] In a patient with unexplained polycythemia, intravenous urography should be done.

In most of the cases studied there were elevated levels of serum or urine erythropoietin,[56,58] which appeared identical with "normal" erythropoietin. Erythropoietin has been isolated from renal cell carcinoma, Wilms tumor, liver cell carcinoma, cerebellar hemangioblastoma and leiomyoma.[56,58] It has also been isolated from renal cyst fluid,[58] which suggests that, at least in some cases, it is produced by adjacent, compressed renal tissue. However, the recurrence of polycythemia with distant metastases[56,58] shows that neoplasms can produce the hormone. An additional possibility is suggested by a case of liver cell carcinoma with a high plasma level of erythropoietin but with none detected in the neoplasm.[58] This patient's liver tissue lacked the normal ability to inactivate erythropoietin.

Erythroid Aplasia

Severe anemia, absence of reticulocytes and a substantial decrease in erythroid cells in the marrow have been associated with thymoma, usually of the spindle-cell type.[59-62] Perhaps 5 percent of thymomas are associated with pure red blood cell aplasia, and occasional cases are also associated with leukopenia or thrombocytopenia.[61] Conversely, a third to a half of adults with erythroid aplasia will have a thymoma; additional cases have been ascribed to marrow injury by drugs or viruses, or in association with pregnancy. Rare cases have been reported in patients with cancer of the lung, stomach or thyroid, as well as with lymphoid neoplasia.[58,62] The mechanism appears to be immunologic, with an IgG antibody directed against the nuclei of erythroblasts.[5,60,63] Myasthenia gravis is usually associated with other histologic types of thymoma, but occasionally the two syndromes coexist.[62] Erythroid aplasia is an unfavorable prognostic sign in thymoma.[64] However, from 15 percent to 29 percent of patients enjoy prolonged remissions following thymectomy,[60,64] and another 15 percent when thymectomy is followed by steroid therapy.[60] Radiotherapy may be of benefit, while androgen therapy has yielded variable results.

Hemolytic Anemia

Coombs-postive hemolytic anemia is a common finding in patients with lymphoid malignancies; it has occasionally been reported in association with other neoplasms,[5] including carcinomas of the ovary,[65] stomach, colon,[66] lung, cervix and breast.[67] The direct Coombs test is positive, a reticulocytosis is present, there may be slight splenomegaly, and steroid therapy may be partially effective. Thus, idiopathic hemolytic anemia may be closely mimicked. In some instances removal of the neoplasm cures the anemia.[65] It seems likely that a substance produced by the neoplasm evokes antibodies which cross-react with red blood cells.[66] Production by the neoplasm of a substance which is toxic to red blood cells has not been observed in humans. Anemia of a microangiopathic type can occur in association with neoplasms; here, however, the direct Coombs test is negative and red blood cell fragmentation is seen.

Thrombocytosis and Leukocytosis

Thrombocytosis is a relatively common finding in association with neoplasms, although precise figures are not available.[56,68-71] Usually thrombocytosis occurs with metastatic disease, especially with marrow involvement; in this situation it may be accompanied by leukocytosis. Occasionally, thrombocytosis may be associated with a localized neoplasm and may subside after its removal; this phenomenon appears to be more common in renal cancer.[56] The platelet count rarely exceeds 1 million per μl but may reach 6 million.[71] Hemor-

rhagic or thrombotic complications are unusual, perhaps because platelet function is normal. A spurious hyperkalemia may accompany thrombocytosis of any cause. Other causes of thrombocytosis include hemorrhage, splenectomy, iron deficiency, recovery from myelosuppression, vincristine therapy, and various infectious and inflammatory disorders. A thrombocytosis-producing factor has been tentatively identified in animal experiments;[56,68,72] its source is unproved.

Leukocytosis is one of the leukoerythroblastic features of the blood that may accompany marrow invasion by a neoplasm. Leukocytosis, sometimes of an extreme degree,[73] is noted occasionally in patients with neoplasms in the absence of overt infection or tumor necrosis.[56,68,73] Eosinophilia[4,68,73] or monocytosis[74] may also occur. Other causes of leukocytosis include lithium and recovery from myelosuppression. A leukocytosis-producing factor has been tentatively identified in animals,[56,68,72] but whether it is produced by neoplastic cells is not known.[4]

Coagulopathies

Intravascular Coagulation

Disseminated intravascular coagulation (DIC) has been reported with a wide variety of neoplasms.[75-77] The clinical features may include thrombocytopenia and a decrease in coagulation factors including fibrinogen and factors V and VIII. The Quick prothrombin time and partial thromboplastin time are prolonged. Platelet plug formation is inhibited. The result is a tendency toward general bleeding. Erythrocyte fragmentation may be a part of the syndrome, or hemolysis may occur without overt DIC.[75] The neoplasms most frequently associated with DIC include acute progranulocytic leukemia and carcinoma of the prostate, as well as mucin-producing adenocarcinomas.[75-77] In addition, DIC may occur as a result of therapy, which may release thromboplastic substances from leukemic and normal leukocytes,[75] or cancer cells.[78] Mucin can activate factor X[75,76] and, unlike tissue thromboplastin, can do so despite a deficiency of factor VII. In other patients there may be diminished survival of fibrinogen in the absence of symptoms. Fibrinolytic activity may be increased secondarily.[75] Primary fibrinogenolysis is unusual except following prostatic operations, but it may be seen in some patients with untreated carcinoma of the prostate.[75] The therapy of DIC is controversial and not uniformly successful; heparin is sometimes effective,[75,79] and spontaneous improvement may occur. Other causes of DIC include sepsis and transfusion reactions;[75] L-asparaginase can cause hypofibrinogenemia. A positive protamine test is supportive of a diagnosis of DIC, but may also be caused by transfusion, traumatic venipuncture or venous thrombosis.[75] Localized intravascular coagulation can occur in cavernous hemangiomas and can result in findings similar to those in the disseminated type.[68]

Venous Thrombosis

Migratory thrombophlebitis was first described by Trousseau. More frequent is venous thrombosis with the risk of pulmonary emboli. A thrombotic tendency has been noted in association with many types of neoplasms, particularly those of the stomach, pancreas, ovary, lung and colon.[5,8,77,80,81] In contrast to the bleeding tendency in acute DIC, chronic DIC may be associated with a thrombotic tendency.[76,77] It is clear that patients with various types of cancer have a tendency to thrombosis; it is less clear that they have a greater tendency than do patients equally ill with benign diseases, although there is evidence that this is so.[77,80] Mucin can activate factor X, and endothelial disruption can activate factor XII.[75] Thrombocytosis may also play a role. In those cases in which the neoplasm could be successfully treated, the thrombotic tendency did not recur.[75]

Sterile Endocarditis

Sterile vegetations on previously normal heart valves may occur in association with a variety of neoplasms, especially mucinous adenocarcinomas.[5,76,81,82] The valves affected are usually on the left side of the heart, which is difficult to explain if the syndrome is caused by substances released into the systemic circulation. Sterile endocarditis occurs in about 20 percent of patients with chronic DIC, and in those in whom it occurs arterial emboli are frequent.[76] A murmur may or may not be heard.[81] The vegetations are composed of platelets and fibrin; occasionally they become secondarily infected.[82] Thrombophlebitis or overt DIC usually does not coexist with sterile endocarditis. The syndrome is seen with chronic nonneoplastic diseases somewhat less frequently than in association with cancer.[82] However, the term marantic is inaccurate; the patients may not be cachectic.

Dysfibrinogenemia

Acquired structural abnormalities in the fibrinogen molecule have been reported in association

with liver cell carcinoma, as well as with cancer metastatic to the liver and benign liver disease.[83] The result is prolongation of prothrombin, thrombin, and partial thromboplastin times, as well as inhibition of the clotting of normal plasma. There is no evidence of factor deficiency or fibrinogenolysis. In most patients there was no clinically important bleeding.

Protein Disorders

Amyloidosis

Amyloid deposition may be associated with myeloma and macroglobulinemia[84,85] and a variety of nonplasmacytic neoplasms,[56] including renal cell and gastric carcinoma as well as Hodgkin and non-Hodgkin lymphoma. In the past, amyloidosis was divided into primary and secondary types on the basis of the organs involved and the underlying condition. It now appears that whatever the underlying condition the pattern of involvement may be similar and may include the blood vessels, heart, carpal tunnel, tongue, gastrointestinal tract, anus, liver, spleen, joints, skin and kidney.[56,84,85] Impairment of organ function, obstruction or bleeding may occur. Factor X deficiency and fibrinogenolysis have been reported. The amyloid seen in association with plasmacytic disorders resembles the light chains of IgG in structure, while that seen in conjunction with other neoplasms contains the "AA" protein.[86] The idea that the protein abnormality reflects an attempt at defense against the nonplasmacytic neoplasm is supported by the following observation. In a patient with renal cell carcinoma there was a spontaneous regression of pulmonary metastasis but renal failure caused by amyloid deposition occurred.[56] Amyloid occurs locally within medullary carcinoma of the thyroid.

Paraproteinemia

Monoclonal gammopathy has been defined as a narrow band on serum protein electrophoresis; at present the term may include the additional requirement that the protein react with either *k*- or λ-antisera but not both, on immunoelectrophoresis. Besides being produced by plasmacytic neoplasms, monoclonal proteins may occur in association with a variety of other neoplasms,[84,87-91] including carcinomas, sarcomas, lymphomas and leukemias. Sometimes these paraproteins show cold-agglutinin or cold-precipitating activity, or both,[84,92] but in most patients they produce no direct symptoms. They may be associated with amyloid deposition. The possibility of a coexisting myeloma should be kept in mind. Each paraprotein appears to be idiotypically unique. However, the paraproteins show no detectable differences at present which would allow one to distinguish between patients with myeloma or macroglobulinemia, those with other neoplasms, and those with no apparent cause for the protein elevation.[91] The differential diagnosis would have to rest on the degree of marrow plasmacytosis, the presence of osteolytic lesions, and the presence or absence of a nonplasmacytic neoplasm.[87]

In some cases, it has been possible to show that the protein is present (and probably produced) in plasmacytes surrounding the carcinoma,[89] which suggests that it may be an antineoplastic antibody.[91] In other cases, the protein has been shown to possess the ability to bind heparin or clotting factors,[91] a situation that could produce a coagulopathy. Some gastrointestinal cancer cells may possess the i-antigen on their surfaces, which might evoke an antibody that agglutinates red blood cells.[92] Besides the possibility that the protein is an antibody directed against an antigen associated with the cancer, and the possibility of a coexisting plasmacytic neoplasm, one might consider the following possibilities. The protein disorder could have rendered the patient more susceptible to the development of a nonplasmacytic neoplasm. On the other hand, the paraprotein and the cancer could have occurred together by chance; perhaps 1 percent of apparently healthy older persons have a monoclonal gammopathy.[91] The disappearance of the gammopathy following removal of a nonplasmacytic neoplasm is extremely rare. A source of confusion is that paraproteins associated with nonplasmacytic neoplasms may be classified as benign monoclonal gammopathies.

Digestive Disorders

Zollinger-Ellison Syndrome

The Zollinger-Ellison syndrome results from non-β cell adenomas or (in 44 percent) carcinomas of the pancreatic islets or duodenum, with production of gastrins (big, little and "mini") by the neoplasm.[4,93] The gastrins cause excessive gastric acid secretion, which results in single or multiple ulcers of the duodenum or jejunum. In addition, in a third of the patients intractable diarrhea develops, perhaps because pancreatic

and intestinal enzymes are inactive at an acid pH. Multiple endocrine neoplasia type 1 (MEN-1) includes gastrinomas or insulinomas as well as parathyroid and pituitary neoplasms. Another dominant condition, MEN-2, consists of medullary carcinoma of the thyroid, pheochromocytoma and parathyroid neoplasms. Those patients who lack parathyroid neoplasms but who have dermal or mucosal neuromas are said to have MEN-2b or MEN-3. However, there is some overlap between MEN-1 and MEN-2.[94]

About 87 percent of cases of the Zollinger-Ellison syndrome result from neoplasms of the islets. There is some doubt that islet cells produce gastrins under normal conditions;[95,96] however, gastrin production by islet cell neoplasms is not usually thought of as being ectopic. There is at least one case report of the Zollinger-Ellison syndrome caused by gastrin production by a mucinous adenocarcinoma of the ovary[97] and another by a ductal adenocarcinoma of the pancreas.[98] Other causes of fasting hypergastrinemia include atrophic gastritis, antral G-cell hyperplasia, retained antrum, impaired function of the kidneys or small intestine and vagotomy without gastrectomy. Routine therapy for ulcer or diarrhea is ineffective.[93] If removal of the neoplasm is impossible, symptomatic therapy with cimetidine may obviate the need for total gastrectomy. Streptozocin therapy may also be useful.

Diarrheal States

Diarrhea often occurs in the Zollinger-Ellison syndrome as well as in the carcinoid syndrome. Non-β islet cell neoplasms may cause "pancreatic cholera" by producting vasoactive intestinal polypeptide (VIP).[99,100] In addition, VIP production and diarrhea have been reported in rare cases of carcinoma of the lung (mainly squamous), as well as pheochromocytoma and ganglioneuroblastoma.[99,100] However, VIP levels require careful interpretation. Prostaglandins[101] and other hormones[4] may also play a role in diarrheal states. Streptozocin or indomethacin therapy may be useful in some patients. Other neoplasms may cause diarrhea by nonhormonal mechanisms. Villous adenoma (or carcinoma) and polyposis of the colon and rectum can cause massive loss of fluid, electrolytes and protein. Adult celiac disease may be associated with an increased incidence of lymphoma;[102] and association with carcinoma of the small intestine has been suggested. The incidence of malabsorption may be increased in cancer patients as a group, but this has not been proved.[5] In this regard, a toxic effect of chemotherapy or irradiation should be considered, as well as mucosal ulceration or lymphatic obstruction by the neoplasm, and amyloid deposition in the bowel wall.[103]

Constipation has not been accepted as a paraneoplastic syndrome. One case has been reported in which constipation and malabsorption were attributed to enteroglucagon present in a renal carcinoma.

Hepatic Dysfunction

Between 10 percent and 14 percent of patients with renal cell carcinoma, but without hepatic metastases, have abnormalities of liver function including elevation of alkaline phosphatase and glutamic-oxaloacetic transaminase levels, reduction in prothrombin activity, reversal of the albumin:globulin ratio, and elevation of Bromsulphalein (sulfobromophthalein sodium) retention.[56,104] Minimal enlargement of the liver may be present, but results of liver biopsies are within normal limits.[104] In those cases in which removal of the neoplasm was accomplished, liver size and function returned to normal. The mechanism is unknown.

Renal Dysfunction

Nephrotic Syndrome

In perhaps 6 percent of patients with the nephrotic syndrome a neoplasm has or will develop.[45,105-107] The syndrome has been associated with Hodgkin and non-Hodgkin lymphoma,[108] as well as carcinomas of the lung, stomach,[109] colon or ovary. The nephrosis may antedate the discovery of the neoplasm; it has been proposed that unexplained nephrosis occurring after the age of 40 should provoke a search for a neoplasm.[45] In some cases nephrosis is caused by invasion of the kidney by neoplastic cells, renal amyloidosis or renal vein thrombosis.[45,108] In other cases an immunologic mechanism is likely. Antigen-antibody complexes have been identified on the glomeruli;[45,105] such complexes may include carcinoembryonic antigen.[105] Viral antigens have been suggested but not proved. Membranous or lobular glomerulonephritis[45] may be present in some patients and minimal-change lesions in others, particularly those with lymphomas.[108] Whether the minimal-change lesion represents an earlier stage is not known.[108] In most cases in

which the neoplasm could be successfully treated, the nephrotic syndrome remitted.[45,105] In one instructive case, both the lung cancer and the nephrotic syndrome remitted with cyclophosphamide therapy. When both the cancer and the nephrosis recurred, cyclophosphamide therapy caused improvement in the nephrosis despite lack of improvement in the cancer. Cyclophosphamide appeared to exert its antineoplastic and immunosuppressive effects independently.

Tubular Defects

Tubular defects of either the proximal or distal types (or both) have been reported in association with multiple myeloma,[5,45,84,110] as well as with idiopathic light-chain proteinuria. The damage to the tubular cells appears to be caused by deposition of light chains. Potassium-losing nephropathy with lysozymuria has been reported in acute nonlymphocytic leukemia.[45,111] However, it is doubtful that lysozyme (muramidase) is the cause of the tubular defect.[112] Its appearance in the urine may be the result of the defect. A proximal tubular defect is sometimes associated with inappropriate secretion of antidiuretic hormone; the mechanism is unknown.[5] Hypokalemic nephropathy may be associated with diarrheal states, production by a neoplasm of aldosterone or renin, Cushing syndrome or renal potassium wasting.[45] Tubular defects may also be caused by therapy with streptozocin, cephalothin or gentamicin.

Musculoskeletal Disorders

Hypertrophic Osteoarthropathy

Hippocrates described curved fingernails, warm fingertips and swollen feet in cases of "empyema." Since that time, hypertrophic osteoarthropathy has been associated with a variety of benign and malignant diseases of the thorax and, less frequently, the abdomen.[5,113-115] Among neoplastic causes lung cancer is the most prominent, but osteoarthropathy is unusual in small cell carcinoma.[13] Other neoplasms affecting the thorax, whether primary or metastatic, benign or malignant, epithelial or lymphoid,[116] may be associated with osteoarthropathy. Intra-abdominal causes are uncommon and include ulcerative colitis[5] as well as carcinoma. In its mildest form osteoarthropathy involves clubbing of the fingers and toes. In more advanced cases there is periosteal new-bone formation visible on bone radiographs and scans. In other cases there may be thickening of the long bones, metacarpals, metatarsals and phalanges. When these changes are associated with a coarsening of the facial features, the clinical characteristics are indistinguishable from those of pachydermoperiostosis,[117] although some reserve this term for the hereditary condition unassociated with thoracic disease. Indeed, the full spectrum from clubbing to pachydermoperiostosis may be hereditary.[117] In most cases associated with a neoplasm, the osteoarthropathy improved when the neoplasm was removed[114] or successfully treated with irradiation or chemotherapy.[116] Clinical features regress more quickly than radiographic signs.

Various mechanisms have been proposed. Neural factors play a role in some patients. In both neoplastic and nonneoplastic conditions, the osteoarthropathy may regress following section of the vagus on the side of the lesion.[5,118] This fact, plus the fact that atropine does not relieve the syndrome,[5] suggests that the vagus carries the afferent limb of the response. The observation that the syndrome may regress after thoracotomy without resection is unexplained. The fact that osteoarthropathy is sometimes associated with estrogen hyperexcretion led to the suggestion that estrogens are causally related.[114] However, the association is inconstant,[5] and osteoarthropathy is not seen with estrogen therapy for breast or prostatic carcinoma. The increased warmth and blood flow of the extremities has suggested a vascular mechanism.[5,119] Neoplasms can produce an angiogenesis factor which may be of great importance in their growth, but its relation to osteoarthropathy remains unproved; limb blood flow may fall after nonresectional surgical procedures.[5] Lung and other neoplasms may contain human growth hormone,[13,120,121] and patients with osteoarthropathy may have acromegaloid features.[114] However, there is no consistent relation between growth hormone levels and the presence or severity of osteoarthropathy.[13,120,121] The same objection applies in the case of neoplasms which contain growth-hormone-releasing hormone.[13,121] Recently, we observed a patient with a malignant mesothelioma in whom both hypoglycemia and osteoarthropathy were manifested. This case is of interest for two reasons. First, osteoarthropathy is said not to occur in malignant mesothelioma.[113] Second, it raises the question of whether somatomedins may be involved in osteoarthropathy as they probably are in hypoglycemia.[19,20,22] One must grant that hypoglycemia and osteoarthropathy coexist un-

commonly; nonetheless, it would be of interest to study somatomedin levels in patients with osteoarthropathy.

Dermatomyositis

The possible association of dermatomyositis and neoplasia has been widely discussed.[5,113,122-125] In large series of patients with dermatomyositis the incidence of malignant neoplasms has been reported variously as 6.7 percent[123] or 16 percent.[124] As has been pointed out, a prospective study would be required to confirm the association.[125] At present, it appears likely that there is some association, particularly when dermatomyositis appears in men after the age of 40.[4,125] The dermatomyositis usually appears within a year of the diagnosis of the neoplasm. Skin manifestations may include erythema or telangiectases of the periorbital region, upper chest or knuckles. Muscle manifestations include proximal-muscle weakness, atrophy and tenderness; they may occur in the absence of skin findings and be diagnosed as polymyositis. The associated neoplasms[125] have included carcinomas of the breast, lung, ovary, and stomach, as well as leukemias, lymphomas and sarcomas. Interestingly, there appears to be a deficit in cases of colorectal carcinoma.[125] Successful therapy for the neoplasm frequently, but not always, is accompanied by improvement in the dermatomyositis.[4,125] However, in the case of chemotherapy, one must consider immunosuppressive as well as antineoplastic effects. The dermatomyositis may respond to steroid therapy,[125] but the response tends to be shorter than in classic dermatomyositis. An immune mechanism is suggested by reports of both humoral[126] and cell-mediated[127] cytotoxicity. Viral-like inclusions have been reported but not cultured. It has been observed that when dermatomyositis accompanies neoplasms, it is more likely to be associated with a motor neuropathy demonstrable by electromyography.[113]

Disorders of the Skin

A wide variety of dermatoses has been reported to occur in association with neoplasia.[2,5,122,128] Dermatomyositis has been mentioned. It is perhaps the best-studied condition, but its association with neoplasia remains in doubt. Prospective studies would be required to establish clearly the association of these conditions with neoplasia.

Acanthosis Nigricans

Acanthosis nigricans is characterized by hyperpigmentation and papillary hypertrophy in the skin folds of the axilla, groin, face, elbows, knees, inframammary area, umbilicus and elsewhere[2,5,128,129] The syndrome may occur in children in an hereditary form unassociated with neoplasia. In adults it has been estimated to be associated with neoplasia in from 25 percent to 100 percent of cases.[2,5,122] Most of the neoplasms associated with acanthosis nigricans have been gastric or other adenocarcinomas.[2] The skin disorder may precede the diagnosis of the neoplasm by many years[122] and rarely improves with treatment of the neoplasm,[2] casting doubt on a direct relationship. In addition, acanthosis nigricans may be seen in association with obesity,[2] diabetes with insulin resistance, pituitary neoplasms and other endocrine disorders, tuberous sclerosis, and therapy with sex hormones or nicotinic acid. Of interest is a case report in which acanthosis nigricans appeared during therapy with a crude preparation of melanocyte-stimulating hormone, cleared when therapy was stopped, and did not recur during therapy with a purified preparation.[130] This observation suggests that the syndrome may be caused by a relatively small compound (presumably a peptide) present in the pituitary. It should be noted that diffuse hyperpigmentation and not acanthosis nigricans is seen in patients with ACTH-producing neoplasms,[2] although acanthosis nigricans has been reported in rare cases of pituitary neoplasms.

Miscellaneous Dermatoses

Pellagra-like lesions may accompany a carcinoid syndrome because of the excessive uptake of tryptophan by the neoplasm.[128] Porphyria cutanea tarda may be associated with liver cell carcinoma or adenoma.[2,131] In most cases the porphyria and the carcinoma both appear to be related to the underlying cirrhosis; however, in a few cases, the adenoma or carcinoma contained much more porphyrin than the adjacent hepatic tissue.[2] A crusting, pustular erythema of the face and skin folds has been reported in a few patients with mild diabetes and glucagon-producing islet cell neoplasms. Pemphigus vulgaris or bullous pemphigoid may be associated with neoplasia in 12 percent of cases.[2,132] An immune mechanism is suggested by the presence of fluorescent antibodies in some cases, as well as by the fact that many of the

neoplasms were lymphoid.[132] However, as with some other dermatoses, some patients were on long-term corticoid therapy before the diagnosis of the neoplasm was made; the therapy, not the dermatosis, may have been the determining factor in the appearance of the neoplasm.

Nodular panniculitis, sometimes accompanied by polyarthropathy, has been reported in association with lipase-containing adenocarcinoma of the pancreas as well as with pancreatitis.[133] Acquired hypertrichosis lagunosa, a diffuse increase in lanugo hair, may accompany various neoplasms as well as diazoxide therapy.[2,5] Erythema gyratum repens is an unusual, rapidly changing erythema in a "wood-grain" or "zebra" pattern; it is said to be strongly associated with neoplasia.[2,5,122] Acquired ichthyosis may accompany various neoplasms.[2,122] Tylosis, a hyperkeratosis of the palms and soles, has been associated with carcinoma of the esophagus in two families; the condition is dominant.[2] It is doubtful that tylosis is related to neoplasia in any other respect.[2] Multiple sebaceous adenomas have been reported in association with visceral carcinomas.

Neurologic Disorders

Neoplasms may involve the nervous system by direct extension, compression, ischemia, metastases, metabolic disturbances or by remote effects.[2,5,134] Perhaps 10 percent of "strokes" prove to be brain metastases. Because there is no effective treatment for the remote effects, every effort should be made to rule out treatable causes of neurologic dysfunction, including metastases, infection, subdural hematoma, angiitis,[135] carotid stenosis,[136] hydrocephalus and emboli. In addition, one should be alert for metabolic disturbances, including hypercalcemia, hyponatremia, hypoglycemia, hyperviscosity, hepatic or renal insufficiency, anemia, and hypoxia, as well as the effects of endogenous or exogenous corticoids or other agents with potential neurotoxicity.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is characterized by progressive weakness of one or more extremities, dementia, disturbances of gait and speech, visual loss, involuntary movements and seizures.[2,5,134,138] Cerebellar or cord signs are unusual. The symptoms usually begin after the underlying disease is well advanced and progress rapidly, with death occurring in two to four months.[137] The electroencephalogram and radionuclide scan may show bilateral abnormalities.[137] Computerized tomographic (CT) scanning has shown bilateral lesions in asymptomatic children who had received cranial irradiation and intrathecal methotrexate; these treatments can be followed by PML. It seems likely that CT scanning will be useful in the early diagnosis of PML.

PML has been reported in patients with leukemia, lymphoma and myeloma; rarely, it may accompany carcinomas or polycythemia vera.[137,138] In addition, PML has been reported in immunosuppressed recipients of organ grafts, as well as in patients with lupus, granulomatous diseases and, very rarely, in previously healthy persons.[137,138]

The resemblance of PML to viral neurologic diseases of animals and humans led to a search for a viral cause. Papova viruses including the JC and SV-40 (simian vacuolating-40) viruses have been recovered from brain tissue of patients with PML.[139-141] The patients from whom the SV-40 virus was recovered had had no known exposure to monkeys. It is conceivable that they received the virus from early lots of "inactivated" polio vaccine, which may have been contaminated with SV-40. The incriminated viruses contain DNA, but clinical trials of idoxuridine and cytarabine (Ara-C) have been disappointing.[142] Vidarabine (Ara-A) has been effective in the treatment of herpes zoster and herpes simplex encephalitis; trials of this agent in PML are awaited with interest. The viruses which have been incriminated in the cause of PML are oncogenic.[138] Bizarre, dysplastic astrocytes are present in many cases of PML.[137] If successful therapy can prolong these patients' survival, the possibility of the development of astrocytoma will have to be kept in mind. It should be noted that even if a viral cause is established, immune mechanisms may aggravate or perpetuate the damage to the brain.

Limbic Encephalopathy

Limbic encephalopathy is also referred to as subacute encephalomyelitis. It is characterized by a subacute onset of cerebral dysfunction, involuntary movements, ocular and bulbar palsy, ataxia, nystagmus, and sensory and motor neuropathy.[143,144] The bulbar and cord findings may be reminiscent of poliomyelitis.[143] The course is more insidious than is the case in PML. The onset may occur before or after the diagnosis of the neoplasm. The syndrome has been reported with carcinomas of the lung, uterus, breast and other sites.[143] The prognosis is usually poor, but im-

provement occurs in some cases. The mechanism is obscure, but there is some evidence for organ-specific antibodies directed against nerve tissue.[143]

Pontine Lesions

Central pontine myelinolysis is characterized by tetraparesis, ocular muscle palsies, pupillary abnormalities and other bulbar signs.[142] The syndrome has been reported in patients with leukemia and, possibly, with other neoplasms. The syndrome may also occur in patients with alcoholism and pancreatitis.[145] Intravenous injection of pancreatic lipase produces demyelination in rabbits; it would be of interest to look for a possible enzymatic mechanism. Pontine lesions may result from cranial irradiation in conjunction with intrathecal methotrexate therapy or (in one patient) in conjunction with systemic therapy with a nitrosourea.

Cerebellar Atrophy

Cerebellar atrophy includes ataxia of the upper and lower extremities, nystagmus, and dysarthria, often accompanied by involvement of the cerebrum, cranial or peripheral nerves, and long tracts.[146,147] It has been associated with carcinomas of the lung, breast, ovary and kidney, as well as Hodgkin and non-Hodgkin lymphoma.[146,147] The onset is often abrupt and the course progressive, although recovery has been reported.[146] The course of the syndrome usually does not parallel that of the neoplasm. The syndrome resembles the viral disease kuru.[146] Fluorouracil and perhaps vincristine may have toxic effects on the cerebellum. The differential diagnosis may also include alcoholism, myxedema, combined-system disease, multiple sclerosis, and the toxic effects of glutethimide and phenytoin.[146] A related syndrome is opsomyoclonus, which is characterized by acute cerebellar ataxia with ataxic eye movement.[148] It may accompany neuroblastoma. It disappears with successful therapy for the neoplasm; for unknown reasons, it appears to be a favorable prognostic sign.

Myelopathy

A poliomyelitis-like lesion of the cord has been the subject of a few reports.[143,149,150] Most of the associated neoplasms have been visceral carcinomas. Metastases to the cord are usually extramedullary. However, they may be intramedullary, in which case the myelogram is usually normal. Distinguishing such a metastasis from a distant effect of cancer would be difficult.[150] Irradiation and intrathecal chemotherapy can cause cord damage including paraplegia.

Neuropathy

Neuropathy involving cranial or peripheral nerves has been reported in association with a variety of epithelial and lymphoid neoplasms.[3,5,143,151,152] In perhaps 16 percent of patients with cancer a neuropathy will develop. The onset of the neuropathy may precede or follow the diagnosis of the neoplasm and the course of the neuropathy may or may not parallel that of the neoplasm.[143] The neuropathy may be motor, in which case it may resemble amyotrophic lateral sclerosis,[162] or it may be sensory, but in most cases it affects both modalities. The differential diagnosis includes amyloid neuropathy caused by amyloid infiltration of the nerves[153] or by compression in the carpal tunnel. In addition, one may consider neuropathy associated with diabetes, tabes, myxedema, uremia or vitamin deficiency. Vincristine, vinblastine, procarbazine and hexamethylmelamine can cause a toxic neuropathy. Corticoid therapy occasionally may improve the neuropathy even in those cases not associated with lymphoid neoplasia.[143] In some cases, there is evidence of antibodies reacting with nerve tissue,[5,154,155] but it is unclear whether they are the cause or the result of neural damage.[5] There is little evidence for a toxic, vitamin-deficiency, or viral mechanism.[5,143] In some patients axonal degeneration is detectable before symptoms appear.[156]

Some forms of neuropathy merit special comment. Neuropathy is reported in occasional patients with polycythemia vera;[2,143] ischemia may be a factor. Irradiation may cause cranial or peripheral neuropathy as a delayed effect. Neuropathy of the brachial plexus may occur as a remote effect of neoplasia;[157] it may also be caused by neoplastic infiltration or irradiation. Abnormalities of taste may be common in patients with cancer and may in part explain anorexia.[158] Autonomic neuropathy with orthostatic hypotension is a rare concomitant of neoplasia.[5,159]

Myasthenia Gravis

About 10 percent of patients with myasthenia gravis have a thymoma, usually of epithelial or mixed type, and an additional 75 percent have thymic hyperplasia.[160-162] Conversely, in about

30 percent of patients with a thymoma myasthenia gravis will develop. Myasthenia gravis has been reported in rare cases of small cell carcinoma of the lung, other carcinomas and lymphomas;[162] however, coexisting thymic disease was not ruled out in all of these reports. In addition, some of the cases may in fact have represented the myasthenic syndrome. Hence, it is doubtful that myasthenia gravis is associated with nonthymic neoplasms more often than can be explained by chance. It should be recalled that the incidence of other neoplasms is probably increased in patients with thymoma.[163] Of patients with myasthenia gravis, 50 percent to 75 percent benefit from thymectomy, although, occasionally, the myasthenia worsens after surgical operation.[160-164] Neostigmine is usually effective. Antibodies binding to acetylcholine receptors have been identified in myasthenia as well as in some patients with thymoma but without myasthenia.[165] Cellular immunity may also play a role.

Myasthenic Syndrome

Eaton and Lambert[166] described a syndrome associated with nonthymic neoplasms, especially small cell carcinoma of the lung. Unlike myasthenia gravis, this syndrome is usually not accompanied by ptosis or respiratory weakness; the tendon reflexes are often reduced, and repeated contraction initially causes increased (not reduced) strength.[162,166] The last characteristic can be noted on an electromyogram and helps to differentiate the syndrome from myasthenia gravis.[162,166,167] A similar electromyogram is produced by botulism and intoxication with neomycin or magnesium.[162,167] However, no toxin has yet been identified in the myasthenic syndrome. The myasthenic syndrome usually does not respond to neostigmine but often responds to guanidine.[5,162,167] The prognosis of small cell lung cancer is improving; it will be interesting to observe the course of the myasthenic syndrome in patients who survive for prolonged periods.

Discussion

There is no hypothesis that can explain all of the remote effects of neoplasia. Nevertheless, some of the data can be made more intelligible using certain hypotheses. These hypotheses are not necessarily mutually exclusive.

Perhaps the most widely applicable hypothesis is that of genetic derepression. It is believed that somatic cells, including neoplastic cells, contain much of the genetic information which was contained in the zygote. This has been seen in amphibians. Nuclei were removed from renal carcinoma cells of frogs and then implanted into enucleated frog ova. Swimming tadpoles developed in about 5 percent of the experiments.[168] The tadpoles were normal in histologic appearance and contained tissues derived from all three germ layers. Similar results were obtained using nuclei removed from normal intestinal epithelial cells, although the success rate was higher than was the case when neoplastic nuclei were used. These data indicate that, at least in this system, some neoplastic cells contain all the genetic information required to form a complete embryo. In addition, the data illustrate that in the proper environment the malignant transformation is reversible. Obviously, most—perhaps 90 percent—of the genetic information present in the zygote is not needed in differentiated somatic cells.[4] The unneeded information must be repressed. Possible mechanisms for this repression involve histone and nonhistone proteins and nuclear RNA. Failure of the repression mechanism is termed derepression.

It is clear that derepression does not occur in a random fashion. As has been mentioned, specific types of neoplasms are more likely to be associated with specific paraneoplastic syndromes. For example, the production of ACTH is more frequently associated with small cell than with squamous carcinoma of the lung.[13] In addition, ectopic hormone production varies from common (in the case of chorionic gonadotropin) to very rare or unknown (in the case of thyrotropin). Further evidence for the selectivity of derepression comes from experiments with neoplasms in animals, which may be characterized by the presence of RNA species not found in the normal, differentiated tissue as well as by the lack of RNA species which are normally present. In this regard, it should be recalled that no neoplasm of a nonendocrine organ has been shown to produce a steroid hormone de novo,[50] although some neoplasms can aromatize C19 precursors to estrogens.[51] The latter ability is possessed by the normal placenta.[52] Perhaps the complex series of steps that de novo steroid hormone synthesis requires is beyond the scope of even a selective derepression. Moreover, with the exception of prostaglandins, all substances known to be produced by neoplasms and to give rise to hormonal effects are proteins or peptides.[4] Hence, derepres-

sion appears to be concerned principally with the synthesis of peptides.

Closely related to the concept of derepression is that of dedifferentiation. Dedifferentiation could involve arrested differentiation, which may be exemplified by teratomas, as well as unbalanced retrodifferentiation, for which there is little direct evidence. Arrested differentiation is sometimes referred to as "blocked ontogeny," but this term implies an abnormality in embryologic development. Congenital neoplasms such as Wilms tumor may be examples of the latter mechanism, but it would be imprecise to refer to a cancer in an elderly person as being the result of blocked ontogeny.

In addition to dedifferentiation of a cell, one must consider dedifferentiation of a tissue.[7] This concept holds that a tissue may be composed of cells in various stages of differentiation. The less differentiated cells may proliferate in a neoplasm of that tissue, leaving the impression that all the cells had dedifferentiated. Evidence for this concept comes from the finding of minute amounts of chorionic gonadotropin[169] and of placental lactogen (chorionic somatomammotropin) in normal testes. The appearance of large amounts of these hormones in the presence of testicular neoplasms might be caused by proliferation of the hormone-containing (and presumably hormone-producing) cells, rather than by dedifferentiation of cells which did not contain the hormones under normal conditions.[7] Chorionic gonadotropin may also occur in the nonmalignant pituitary and other tissues,[170,171] raising the question of whether its presence is characteristic of malignant cellular proliferation or of proliferation in general.[1,4,170,172] The latter possibility seems analogous to the presence of minute amounts of carcinoembryonic antigen in normal gut secretions and its increase in inflammatory bowel diseases, or to the appearance of α-fetoprotein in the circulation during recovery from hepatitis. There are reports of chorionic gonadotropin becoming transiently detectable after a surgical procedure when it was undetectable before the operation[173] thus suggesting an association with benign proliferation. Of interest in this connection is the finding of ACTH (mainly "big") in the nonmalignant but abnormal lung of a dog exposed to smoke and in patients with chronic obstructive pulmonary disease.[12] In addition, plasma levels of ACTH tend to be inversely proportional to the degree of differentiation in lung cancer.[13] In further support of dedifferentiation of a tissue, is the finding, using the immunoperoxidase technique, that chorionic gonadotropin is present in some, but not all, cells of testicular neoplasms.[174] In addition, when two or more *tumor markers* are present simultaneously, their plasma levels may vary in a discordant fashion,[7] which suggests (but does not prove) that they are produced by different cell lines which have different susceptibilities to therapy. However, these data could be interpreted to suggest that the neoplasm contained cells in varying stages of dedifferentiation. Moreover, islet cell carcinomas may produce chorionic gonadotropin or either of its subunits, none of which is detectable in benign islet cell neoplasms.[171] This observation suggests the dedifferentiation of cells rather than of the tissue as a whole.

A further complication is introduced by the possibility that malignant cells may induce surrounding cells to differentiate along lines they normally would not follow.[175] Conceivably, the latter cells might give rise to some paraneoplastic syndromes. Messenger RNA from a human neoplasm can induce in amphibian ova the synthesis of a polypeptide which reacts with antibodies to both calcitonin and carcinoembryonic antigen.[176] If this observation can be confirmed, it suggests that neoplastic cells may produce, or induce surrounding cells to produce, pluripotential prohormones, which are converted to various hormones depending on the enzymatic content of the cell in question.[176] Tumor-host cell hybridization may occur in vivo and is demonstrable in vitro.[177] Such hybrids may produce gene products of either parent cell as well as gene products not present in either parent cell.[177] Hybridization might possibly explain some paraneoplastic syndromes, as well as the mixture of histologic patterns present in some neoplasms[177] or perhaps some instances of drug resistance. Most intriguing is a report that bacteria isolated from patients with cancer appear to contain (and perhaps synthesize) a protein resembling chorionic gonadotropin.[178] The ramifications of such genetic exchange remain to be explored and verified.

Attempts to explain why certain neoplasms are more likely to be associated with certain syndromes have involved classifications based on the presumed embryologic origins of the neoplasms. Pearse and others[6,7,10,11,179] developed the important concept of the APUD system of cells, which share the attributes of amine content, amine precursor uptake and decarboxylation. These cells

share histochemical and ultrastructural characteristics and include the anterior pituitary, autonomic neurons, adrenal medulla thyroid C-cells, islets, and bronchial and gastrointestinal endocrine cells. It was thought that they also shared a neuroectodermal origin. However, it now appears that the islet cells and the bronchial and gastrointestinal endocrine cells are probably of endodermal origin.[180] The parathyroid glands may be of neuroectodermal origin but do not share the APUD characteristics.[180] It is tempting to assume that, for example, small cell carcinoma of the lung arises from bronchial endocrine cells and, hence, may produce anterior pituitary hormones.[6,7] However, the origin of small cell carcinoma has been disputed;[13,181] even if it does originate in the bronchial endocrine cells, these cells probably do not arise from the same germ layer as does the anterior pituitary.[180] Moreover, ectopic production of parathormone has been reported in neoplasms of all three germ layers.[2,5-9] Hence, attempts to correlate ectopic hormone production with embryologic origin have not yet been uniformly successful, particularly when one considers that a single neoplasm may produce up to eight hormones.[2]

Immunologic mechanisms may be related to some paraneoplastic syndromes such as hemolytic anemia, nephrotic syndrome, and some neurologic manifestations.[4,182-184] Several relationships are possible. The immunologic disorder and the neoplasm may occur together by chance; aging is accompanied by an increasing incidence of both. The neoplasm may expose new or previously hidden antigens such as mucin in enteric cancer or casein in breast cancer.[185] These "forbidden contacts" may evoke immune phenomena.[184] On the other hand, the immunologic abnormality may predispose to the development of a neoplasm, as is the case with immunosuppressive therapy. Finally, the immunologic disease may be a temporarily successful host defense against the neoplasm, with cross-reactivity against normal tissues;[184] ulcerative colitis and Hashimoto thyroiditis are possible examples of this mechanism, but direct evidence is lacking.

Another mechanism which has been suggested is random peptide synthesis—that is, that neoplastic cells assemble amino acids at random, sometimes producing a functional peptide by chance. It is most unlikely that neoplastic cells could fortuitously synthesize enough of even a small peptide to have a clinically apparent effect. In addition, if this mechanism existed, one would expect to find peptides with biologic effects similar to those of existing hormones, but which differed substantially from them in amino acid sequence. Such peptides have not been found.

The production of chorionic gonadotropin merits further comment, in that it may shed light on the "fetal" nature of neoplasia. When only insensitive assays were available, this hormone was detected in patients with trophoblastic disease and germinal neoplasms, as well as in pregnancy. As more sensitive assays were employed, chorionic gonadotropin was reported in association with a variety of neoplasms.[186] When still more sensitive assays were used, the hormone was found in association with many, and perhaps even all, neoplasms.[1,4] The synthesis of each subunit appears to be under the control of a separate gene.[187] The α subunit is virtually identical in chorionic gonadotropin and in follicle-stimulating hormone, luteinizing hormone and thyrotropin, whereas each hormone contains a distinctive β subunit.[1,4] These facts only partially explain why neoplasms are so often associated with chorionic gonadotropin and so rarely (if ever) with the other three glycopeptide hormones.[1,4]

The association of chorionic gonadotropin and other "embryonic" proteins with neoplasia is fascinatingly (and perhaps embarrassingly) reminiscent of Beard's "trophoblastic theory" of malignancy, which dates to 1902[188] and may have been based on still earlier work of Conheim. Beard held that "wandering germ cells of early life could later be activated to divide and produce trophoblast cells which, outside the canalization of pregnancy, are the malignant cells." It is no longer believed that all cancers are derived from such cells. Recent data regarding chorionic gonadotropin, however, suggest that many somatic cells—and perhaps all which are capable of replication—carry within their "genetic library" the information needed to reactivate embryonic mechanisms and, under proper conditions, to produce a neoplasm.

REFERENCES

1. Odell W, Wolfsen A, Yoshimoto Y, et al: Ectopic peptide synthesis, a universal concomitant of neoplasia. Trans Assoc Am Physicians 90:204-227, 1977

2. Waldenstrom JG: Paraneoplasia—Biological Signals in the Diagnosis of Cancer. New York, Wiley, 1978

3. Hall TC (Ed): Paraneoplastic syndromes. Ann NY Acad Sci 230:1-577, 1974

4. Odell WD, Wolfsen AR: Humoral syndromes associated with cancer. Annu Rev Med 29:379-406, 1978

5. Anderson G: Paramalignant syndromes, *In* Baron DN, Compton N, Dawson AM, et al (Eds): Recent Advances in Medicine. London, Churchill Livingstone, 1973, pp 1-29

6. Levine RJ, Metz SA: A classification of ectopic hormone-producing tumors. Ann NY Acad Sci 230:533-546, 1974

7. Baylin SB: Ectopic production of hormones and other products by tumors. Hosp Prac 10:117-126, 1975

8. Odell WD, Wolfsen A: Ectopic hormone secretion by tumors, *In* Becker FF: Cancer—A Comprehensive Treatise—Vol. 3. New York, Plenum Press, 1975, pp 81-97

9. Rosen SW, Weintraub BD: Humours, tumors, and caveats (Editorial). Ann Intern Med 82:274-276, 1975

10. Azzopardi JG, Williams ED: Pathology of "nonendocrine" tumors associated with Cushing's syndrome. Cancer 22:274-286, 1968

11. Imura H, Matsukura S, Yamamoto H, et al: Studies on ectopic ACTH-producing tumors—II. Clinical and biochemical features of 30 cases. Cancer 35:1430-1437, 1975

12. Gewirtz G, Yalow RS: Ectopic ACTH production in carcinoma of the lung. J Clin Invest 53:1022-1032, 1974

13. Yesner R: Spectrum of lung cancer and ectopic hormones, *In* Sommers SC: Pathology Annual, Part I, Vol 13. New York, Appleton-Century-Crofts, 1978, pp 217-240

14. Corrigan DF, Schaaf M, Whaley RA, et al: Selective venous sampling to differentiate ectopic ACTH secretion from pituitary Cushing's syndrome. N Engl J Med 296:861-862, 1977

15. Yalow RS, Berson SA: Characteristics of "big ACTH" in human plasma and pituitary extracts. J Clin Endocrinol Metab 36:415-423, 1973

16. Upton GV, Amatruda TT: Evidence for the presence of tumor peptides with corticotropin-releasing-factor-like activity in the ectopic ACTH syndrome. N Engl J Med 285:419-424, 1971

17. Marks LJ, Steinke J, Podolsky S, et al: Hypoglycemia associated with neoplasia. Ann NY Acad Sci 230:147-160, 1974

18. Nissan S, Bar-Moor A, Shafrir E: Hypoglycemia associated with extrapancreatic tumors. N Engl J Med 278:177-183, 1968

19. Megyesi K, Kahn C, Roth J, et al: Circulating NSILAs in man. J Clin Endocrinol Metab 41:475-484, 1975

20. Hyodo T, Megyesi K, Kahn C, et al: Adrenocortical carcinoma and hypoglycemia: Evidence for production of nonsuppressible insulin-like activity by the tumor. J Clin Endocrinol Metab 44: 1175-1184, 1977

21. Cahill GF: Hyperglycemia. Ann NY Acad Sci 230:161-167, 1974

22. Goodman MA, McMaster JH, Drash AL, et al: Metabolic and endocrine alterations in osteosarcoma patients. Cancer 42: 603-610, 1978

23. Benson RC Jr, Riggs BL, Pickard BM, et al: Radioimmunoassay of parathyroid hormone in hypercalcemic patients with malignant disease. Am J Med 56:821-826, 1974

24. Powell D, Singer FR, Murray TM, et al: Nonparathyroid humoral hypercalcemia in patients with neoplastic diseases. N Engl J Med 289:176-181, 1973

25. Terz JJ, Estep H, Bright R, et al: Primary oropharyngeal cancer and hypercalcemia. Cancer 33:334-339, 1974

26. Bender RA, Hansen H: Hypercalcemia in bronchogenic carcinoma—A prospective study of 200 patients. Ann Intern Med 80: 205-208, 1974

27. Lee DBN, Zawada ET, Kleeman CR: The pathophysiology and clinical aspects of hypercalcemic disorders (Medical Progress). West J Med 129:278-320, 1978

28. Habener JF, Potts JT: Biosynthesis of parathyroid hormone (second of two parts). N Engl J Med 299:635-644, 1978

29. Seyberth HW, Segre GV, Morgan JL, et al: Prostaglandins as mediators of hypercalcemia associated with certain types of cancer. N Engl J Med 293:1278-1283, 1975

30. Demers LM, Allegra JC, Harvey HA, et al: Plasma prostaglandins in hypercalcemic patients with neoplastic disease. Cancer 39:1159-1162, 1977

31. Husby G, Strickland RG, Rigler GL, et al: Direct immunochemical detection of prostaglandin-E and cyclic nucleotides in human malignant tumors. Cancer 40:1629-1642, 1977

32. Tashjian AH Jr: Role of prostaglandins in the production of hypercalcemia by tumors. Cancer Res 38:4138-4141, 1978

33. Munday GR: Evidence for the secretion of an osteoclast stimulating factor in myeloma. N Engl J Med 291:1046-1051, 1974

34. Munday GR: Bone resorbing activity in supernatants from lymphoid cell lines. N Engl J Med 290:867-871, 1974

35. Mazzaferri EL, D'Orisio TM, LoBuglio AF: Treatment of hypercalcemia associated with malignancy. Semin Oncol 5:141-153, 1978

36. Deftos LJ, Neer R: Medical management of the hypercalcemia of malignancy. Annu Rev Med 25:323-331, 1974

37. Singer FR, Bethune JE, Massry SG: Hypercalcemia and hypocalcemia. Clin Nephrol 7:154-162, 1977

38. Paget disease of the bone—Medical Staff Conference, University of California, San Francisco. West J Med 129:210-224, 1978

39. Raisz LG, Luben RA, Mundy GR, et al: Effect of osteoclast activating factor from human leukocytes on bone metabolism. J Clin Invest 56:408-413, 1975

40. Tashjian AH Jr, Voelkel EF, McDonough J, et al: Hydrocortisone inhibits prostaglandin production by mouse fibrosarcoma cells. Nature 258:739-741, 1975

41. Salassa RM, Jowsey J, Arnaud CD: Hypophosphatemic osteomalacia associated with "nonendocrine" tumors. N Engl J Med 283:65-70, 1970

32. Silva OL, Becker KY, Primack A, et al: Ectopic production of calcitonin by oat cell carcinoma. N Engl J Med 290:1122-1124, 1974

43. Hall TC, Griffiths CT, Petranek JR: Hypocalcemia—An unusual metabolic complication of breast cancer. N Engl J Med 275:1474-1476, 1966

44. Bartter FC: The Syndrome of Inappropriate Secretion of Antidiuretic Hormone. Chicago, Year Book Medical Publishers, 1973

45. Fichman M, Bethune J: Effects of neoplasms on renal electrolyte function. Ann NY Acad Sci 230:448-472, 1974

46. Inappropriate antidiuretic hormone secretion—Medical Staff Conference, University of California, San Francisco. West J Med 122:145-149, 1975

47. Forrest JN, Cox M, Hong C, et al: Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. N Engl J Med 298: 173-177, 1978

48. Moertel CG, Beahrs OH, Woolner LB, et al: Malignant carcinoid syndrome associated with non-carcinoid tumors. N Engl J Med 273:244-248, 1965

49. Stepanas AV, Samaan NA, Schultz PN, et al: Endocrine studies in testicular tumor patients with and without gynecomastia. Cancer 41:369-376, 1978

50. Kew MC, Kirschner MA, Abrahams GE, et al: Mechanism of feminization in primary liver cancer. N Engl J Med 296:1084-1088, 1977

51. Kirschner MA, Cohen FB, Jesperson D: Estrogen production and its origin in man with gonadotropin-producing neoplasm. J Clin Endocrinol Metab 39:112-118, 1974

52. Jones KL: Feminization, virilization, and precocious sexual development that results from neoplastic processes. Ann NY Acad Sci 230:195-203, 1974

53. Braunstein GD, Bridson WE, Glass A, et al: In vivo and in vitro production of human chorionic gonadotropin and alpha-fetoprotein by a virilizing hepatoblastoma. J Clin Endocrinol 35: 857-862, 1972

54. Higgins HP, Hershman JM, Kenimer JG, et al: The thyrotoxicosis of hydatidiform mole. Ann Intern Med 83:307-311, 1975

55. Cave WT, Dunn JT: Choriocarcinoma with hyperthyroidism: Probable identity of the thyrotropin with human chorionic gonadotropin. Ann Intern Med 85:60-63, 1976

56. Chisholm GD: Nephrogenic ridge tumors and their syndromes. Ann NY Acad Sci 230:403-423, 1974

57. Genest J, Rojo-Ortega JM, Kurchel O, et al: Malignant hypertension with hypokalemia in a patient with a renin-producing pulmonary carcinoma. Trans Assoc Am Physicians 88:192-201, 1975

58. Hammond D, Winnick S: Paraneoplastic erythrocytosis and ectopic erythropoietins. Ann NY Acad Sci 230:219-227, 1974

59. Mitchell AB, Pinn G, Pegrum GD: Pure red-cell aplasia and carcinoma. Blood 37:594-597, 1971

60. Krantz SB: Pure red-cell aplasia. N Engl J Med 291:345-350, 1974

61. DeSevilla E, Forrest JV, Zivnuska FR, et al: Metastatic thymoma with myasthenia gravis and pure red-cell aplasia. Cancer 36:1154-1157, 1975

62. LeGolvan DP, Abell MR: Thymomas. Cancer 39:2142-2157, 1977

63. Krantz SB, Moore WH, Zaentz SD: Studies on red-cell aplasia—V. Presence of erythroblast cytotoxicity in gamma-G globulin fraction of plasma. J Clin Invest 52:324-327, 1973

64. Batata MA, Martini N, Huvos AG, et al: Thymomas: Clinicopathologic features, therapy, and prognosis. Cancer 34:389-396, 1974

65. Dawson MA, Talbert W, Yarbro JW: Hemolytic anemia associated with an ovarian tumor. Am J Med 50:552-556, 1971

66. Miura AB, Shibata A, Akihama T, et al: Autoimmune hemolytic anemia associated with colon cancer. Cancer 33:111-114, 1974

67. Sohier WD Jr, Juranies E, Aub JC: Hemolytic anemia, a host response to malignancy. Cancer Res 17:767-774, 1957

68. Waldenstrom JG: Paraneoplasia—Biological Signals in the Diagnosis of Cancer. New York, Wiley, 1978, pp 48-50

69. Traunum BL, Haut A: Thrombocytosis—Platelet kinetics in neoplasia. J Lab Clin Med 84:615-620, 1974

70. Silvis SE, Turklas N, Duscherholman A: Thrombocytosis in patients with lung cancer. JAMA 211:1852-1855, 1970

71. Spigel SC, Mooney LR: Extreme thrombocytosis associated with malignancy. Cancer 39:339-341, 1977

72. Liebelt RA, Gehring G, Delmonte L, et al: Paraneoplastic syndromes in experimental animal model systems. Ann NY Acad Sci 230:547-564, 1974

73. Robinson WA: Granulocytosis in neoplasia. Ann NY Acad Sci 230:212-218, 1974

74. Barrett O Jr: Monocytosis in malignant disease. Ann Intern Med 73:991-992, 1970

75. Goodnight SH Jr: Bleeding and intravascular clotting in malignancy: A review. Ann NY Acad Sci 230:271-288, 1974

76. Case records of the Massachusetts General Hospital (Case 13-1978). N Engl J Med 298:786-792, 1978

77. Pineo GF, Brain MC, Gallus AS, et al: Tumors, mucus production, and hypercoagulability. Ann NY Acad Sci 230:262-270, 1974

78. Harada T, Makisaka Y, Nishimura H, et al: Complete necrotization of hepatocellular carcinoma by chemotherapy and subsequent intravascular coagulation—A case report. Cancer 42: 67-73, 1978

79. Kazmier F, Bowie EJ, Hagedorn A, et al: Treatment of intravascular coagulation and fibrinolysis (ICF) syndromes. Mayo Clin Proc 49:665-672, 1974

80. Davis RB, Theoglides A, Kennedy BJ: Comparative studies of blood coagulation and platelet aggregation in patients with cancer and non-malignant diseases. Ann Intern Med 71:67-80, 1969

81. Troncale FJ: Distant manifestations of colonic carcinoma. Ann NY Acad Sci 230:332-338, 1974

82. Rosen P, Armstrong D: Nonbacterial thrombotic endocarditis in patients with malignant diseases. Am J Med 54:23-29, 1973

83. Gralnick HR, Givelber H, Abrams E: Dysfibrinogenemia associated with hepatoma. N Engl J Med 299:221-226, 1978

84. Salmon SE: "Paraneoplastic" syndromes associated with monoclonal lymphocyte and plasma cell proliferation. Ann NY Acad Sci 230:228-239, 1974

85. Glenner GG, Terry WD, Isersky C: Amyloidosis: Its nature and pathogenesis. Semin Hematol 10:65-86, 1973

86. Levin M, Franklin EC, Frangione B, et al: The amino acid sequence of a major immunoglobulin component of some amyloid fibrils. J Clin Invest 51:2773-2776, 1972

87. Waldenstrom JG: Benign monoclonal gammopathy, *In* Williams WJ, Beutler E, Erslev AJ, et al: Hematology, 2nd Ed. New York, McGraw-Hill, 1977, pp 988-991

88. Alexanian R: Monoclonal gammopathy in lymphoma. Arch Intern Med 135:62-66 1975

89. Solomon A: Bence-Jones proteins and light chains of immunoglobulins. N Engl J Med 294:91-98, 1976

90. Isobe T, Osserman EF: Pathologic conditions associated with plasma cell dyscrasias: A study of 806 cases. Ann NY Acad Sci 190:507-518, 1971

91. Solomon A: Homogeneous (monoclonal) immunoglobulins in cancer (Editorial). Am J Med 63:169-176, 1977

92. Pruzanski W, Shumak KH: Biologic activity of cold-reacting autoantibodies. N Engl J Med 297:583-589, 1977

93. Ellison EH, Wilson SD: The Zollinger-Ellison syndrome: Reappraisal and evaluation of 260 registered cases. Ann Surg 160: 512-516, 1964

94. Cameron D, Spiro HM, Landsberg L: Zollinger-Ellison syndrome with multiple endocrine adenomatosis type II (Letter). N Engl J Med 299:152-153, 1978

95. Creutzfeldt W, Arnold R, Creutzfeldt C, et al: Pathomorphologic, biochemical and diagnostic aspects of gastrinomas (Zollinger-Ellison syndrome). Hum Pathol 6:47-76, 1975

96. Lotstra F, van der Loo W, Gepts W: Are gastrin-cells present in mammalian pancreatic islets? Diabetologia 10:291-302, 1974

97. Cocco AE, Conway SJ: Zollinger-Ellison syndrome associated with ovarian mucinous cystadenocarcinoma. N Engl J Med 293:485-486, 1975

98. Mihas AA, Ceballos R, Mihas A, et al: Zollinger-Ellison syndrome associated with ductal adenocarcinoma of the pancreas. N Engl J Med 298:144-146, 1978

99. Said SI, Faloona GR: Elevated plasma and tissue levels of vasoactive intestinal polypeptide in the watery-diarrhea syndrome due to pancreatic, bronchogenic, and other tumors. N Engl J Med 293:155-160, 1975

100. Soergel KH: Hormonally mediated diarrhea (Editorial). N Engl J Med 292:970-972, 1975

101. Jaffe BM, Condon S: Prostaglandins E and F in endocrine diarrheagenic syndromes. Ann Surg 184:516-524, 1976

102. Harris OD, Cooke WT, Thompson H, et al: Malignancy in adult coeliac disease and idiopathic steatorrhea. Am J Med 42: 899-912, 1967

103. Waldmann TA, Broder S, Strobe W: Protein-losing enteropathies in malignancy. Ann NY Acad Sci 230:306-317, 1974

104. Ramos CV, Taylor HD: Hepatic dysfunction associated with renal carcinoma. Cancer 29:1287-1292, 1972

105. Hopper J Jr: Tumor-related renal lesions (Editorial). Ann Intern Med 81:550-551, 1974

106. Case records of the Massachusetts General Hospital (Case 6-1978). N Engl J Med 298:387-396, 1978

107. Gagliano RG, Costanzi JJ, Beathard GA, et al: The nephrotic syndrome associated with neoplasia, an unusual paraneoplastic syndrome: Report of a case and review of the literature. Am J Med 60:1026-1031, 1976

108. Routledge RC, Hann IM, Morris Jones PH: Hodgkin's disease complicated by the nephrotic syndrome. Cancer 38:1735-1740, 1976

109. Cantrell EG: Nephrotic syndrome cured by removal of gastric carcinoma. Br Med J 2:739-740, 1969

110. Finkel PN, Kronenberg K, Pesce AJ, et al: Adult Fanconi syndrome, amyloidosis and marked kappa-light chain proteinuria. Nephron 10:1-24, 1973

111. O'Regan S, Carson S, Chesney RW, et al: Electrolyte and acid-base disturbances in the management of leukemia. Blood 49: 345-353, 1977

112. Klockars M, Azar HA, Hermida R, et al: The relationship of lysozyme to the nephropathy in chloroleukemic rats and the effects of lysozyme loading on normal rat kidneys. Cancer Res 34:47-60, 1974

113. Mills JA: A spectrum of organ systems that respond to cancer: The joints and connective tissue. Ann NY Acad Sci 230: 443-447, 1974

114. Hammersten JF, O'Leary J: The features and significance of hypertrophic osteoarthropathy. Arch Intern Med 99:431-441, 1957

115. Coury C: Hippocratic fingers and hypertrophic osteoarthropathy—A study of 350 cases. Br J Dis Chest 54:202-204, 1960

116. Atkinson MK, McElwain TJ, Peckham MJ, et al: Hypertrophic pulmonary osteoarthropathy in Hodgkin's disease—Reversal with chemotherapy. Cancer 38:1729-2734, 1976

117. Rimoin DL: Pachydermoperiostosis (idiopathic clubbing and periostosis). N Engl J Med 272:923-931, 1965

118. Flavel G: Reversal of pulmonary hypertrophic osteoarthropathy by vagotomy. Lancet 1:260, 1956

119. Turner-Warwick M: Systemic arterial patterns in the lung and clubbing of the fingers. Thorax 18:238-230, 1963

120. Beck C, Berger HG: Evidence for the presence of immunoreactive growth hormone in cancers of the lung and stomach. Cancer 30:75-79, 1972

121. Case records of the Massachusetts General Hospital (Case 38-1978). N Engl J Med 299:707-714, 1978

122. Curth HO: How and why the skin reacts. Ann NY Acad Sci 230:435-442, 1974

123. Christianson HB, Brusting LA, Perry HO: Dermatomyositis —Unusual features, complications, and treatment. Arch Dermatol 74:581-589, 1956

124. Williams RC: Dermatomyositis and malignancy—A review of the literature. Ann Intern Med 50:1174-1181, 1959

125. Barnes BE: Dermatomyositis and malignancy—A review of the literature. Ann Intern Med 84:68-76, 1976

126. Curtis AC, Hackaman JG, Wheeler AH: Study of the autoimmune reaction in dermatomyositis. JAMA 178:571-573, 1961

127. Dawkins RL, Mastaglia FL: Cell mediated cytotoxicity to muscle in polymyositis. N Engl J Med 288:434-438, 1973

128. Braverman IM: Skin Signs of Systemic Disease. Philadelphia, WB Saunders, 1970

129. Brown J, Winkelmann RK: Acanthosis nigricans: A study of 90 cases. Medicine (Balt) 47:33-51, 1968

130. Nordlund JJ, Lerner AB: Cause of acanthosis nigricans (Letter). N Engl J Med 293:200, 1975

131. Gluckman JB, Turner MD: Systemic manifestations of tumors of the small gut and liver. Ann NY Acad Sci 230:318-331, 1974

132. Bierman SM, Krain LS: Pemphigus vulgaris and internal malignancy. Cancer 33:1091-1099, 1974

133. Mullin GT, Caperton EM, Crespin SR, et al: Arthritis and skin lesions resembling erythema nodosum in pancreatic disease. Ann Intern Med 68:75-88, 1968

134. Brain WR, Norris FH Jr (Eds): The Remote Effects of Cancer on the Nervous System. New York, Grune and Stratton, 1965

135. Greco FA, Kolins J, Rajjoub RK, et al: Hodgkin's disease and granulomatous angiitis of the central nervous system. Cancer 38:2027-2032, 1976

136. Conomy JP, Kellermeyer RW: Delayed cerebrovascular consequences of therapeutic radiation—A clinicopathologic study of a stroke associated with radiation-induced carotid arteriopathy. Cancer 36:1702-1708, 1975

137. Richardson EP: Progressive multifocal leukoencephalopathy, *In* Vinken PJ, Bruyn GW (Eds): Handbook of Clinical Neurology —Vol 9, Multiple Sclerosis and Other Demyelinating Diseases. New York, American Elsevier, 1970, pp 485-499

138. Richardson EP: Our evolving understanding of progressive multifocal leukoencephalopathy. Ann NY Acad Sci 230:358-364, 1974

139. Padgett BL, Walker DL, ZuRhein GM, et al: Cultivation of papova-like virus from human brain with progressive multifocal leukoencephalopathy. Lancet 1:1257-1260, 1971

140. Narayan O, Penney JB, Johnson RT, et al: Etiology of progressive multifocal leukoencephalopathy—Identification of papovavirus. N Engl J Med 289:1278-1282, 1973

141. Martin MA, Gelb LD, Garon C, et al: Characterization of "heavy" and "light" SV40-like particles from a patient with PML. Virology 59:179-189, 1974

142. Canning B, Kobayashi RM, Kaplan CG, et al: Progressive multifocal leukoencephalopathy. West J Med 125:364-369, 1976

143. Henson RA, Urich H: Peripheral neuropathy associated with malignant disease, *In* Vinken PJ, Bruyn GW (Eds): Handbook of Clinical Neurology—Vol 8, Diseases of Nerves. New York, American Elsevier, 1970 pp 131-148

144. Corsellis JAN, Goldberg GJ, Norton AR: "Limbic encephalitis" and its association with carcinoma. Brain 91:481-496, 1968

145. Vogel FS: Conundrum of central pontine myelinolysis, *In* Sommers SC (Ed): Pathology Annual, Part 1, Vol. 13. New York, Appleton-Century-Crofts, 1978, pp 29-39

146. Mancall EL: Late (acquired) cortical cerebellar atrophy, *In* Vinken PJ, Bruyn GW (Eds): Handbook of Clinical Neurology Vol 21, System Disorders and Atrophies. New York, American Elsevier, 1975, pp 477-508

147. Dreyfus PM, Oshtory M, Gardner ED, et al: Cerebellar ataxia: Anatomical, physiological and clinical implications. West J Med 128:499-511, 1978

148. Altman AJ, Baehner RL: Favorable prognosis for survival in children with coincident opsomyoclonus and neuroblastoma. Cancer 37:846-852, 1976

149. Case records of the Massachusetts General Hospital (Case 42-1970). N Engl J Med 283:806-814, 1970

150. Case records of the Massachusetts General Hospital (Case 26-1976). N Engl J Med 294:1447-1454, 1976

151. McLeod JG, Walsh JC: Peripheral neuropathy associated with lymphomas and other reticuloses, *In* Dyck PJ, Thomas PK, Lambert EH (Eds): Peripheral Neuropathy. Philadelphia, WB Saunders, 1975, pp 1314-1325

152. McLeod JG: Carcinomatous neuropathy, *In* Dyck PJ, Thomas PK, Lambert EH (Eds): Peripheral Neuropathy. Philadelphia, WB Saunders, 1975, pp 1301-1313

153. Cohen AS, Benson MD: Amyloid neuropathy, *In* Dyck PJ, Thomas PK, Lambert EH (Eds): Peripheral Neuropathy. Philadelphia, WB Saunders, 1975, pp 1067-1091

154. Wilkinson PC, Zeromski J: Immunofluorescent detection of antibodies against neurones in sensory carcinomatous neuropathy. Brain 88:529-538, 1965

155. Levine GB, Mills PE Jr, Epstein WV: Circulating I_gG globulin and anti-I_gG globulin complex in a patient with carcinoma of the lung and severe neuromyopathy. J Lab Clin Med 69:749-757, 1967

156. Schlaepfer WW: Axonal degeneration in the sural nerves of cancer patients. Cancer 34:371-381, 1974

157. Pezzinenti JF, Bruckner HW, DeConti RC: Paralytic brachial plexus neuritis in Hodgkin's disease. Cancer 31:626-629, 1973

158. DeWys WD, Walters K: Abnormalities in taste sensation in cancer patients. Cancer 36:1888-1896, 1974

159. Siemsen JK, Meister L: Bronchogenic carcinoma associated with severe orthostatic hypotension. Ann Intern Med 58:669-676, 1963

160. Wilkins EW Jr, Edmunds LH Jr, Castleman B: Cases of thymoma at the Massachusetts General Hospital. J Thorac Cardiovasc Surg 52:322-330, 1966

161. Myasthenia gravis and the thymus gland—Medical Staff Conference, University of California, San Francisco. West J Med 123:123-127, 1975

162. Tyler HR: Paraneoplastic syndromes of nerve, muscle, and neuromuscular junction. Ann NY Acad Sci 230:348-357, 1974

163. Papatestas AE, Genkins G, Horowitz SH, et al: Thymectomy in myasthenia gravis: Pathologic, clinical, and electrophysiologic correlations. Ann NY Acad Sci 274:555-573, 1976

164. Perlo V, Arnason B, Proskanzer D, et al: The role of thymectomy in the treatment of myasthenia gravis. Ann NY Acad Sci 183:308-315, 1971

165. Drachman DB, Angus CW, Adams RN, et al: Myasthenic antibodies cross-link acetylcholine receptors to accelerate degradation. N Engl J Med 298:1116-1122, 1978

166. Eaton LM, Lambert EH: Electromyography and electric stimulation of nerves in diseases of motor unit. JAMA 163:1117-1124, 1957

167. Fukuhara N, Takamori M, Gutmann L, et al: Eaton-Lambert syndrome: Ultrastructural study of the motor end-plates. Arch Neurol 27:67-78, 1972

168. McKinnell RG, Deggins GA, Labat DD: Transplantation of pluripotential nuclei from triploid frog tumors. Science 165:394-396, 1969

169. Braunstein GD, Rasor J, Wade ME: Presence in normal human testes of chorionic-gonadotropin-like substance distinct from human luteinizing hormone. N Engl J Med 293:1339-1343, 1975

170. Odell WD: Glycopeptide hormones and neoplasms (Editorial). N Engl J Med 297:609-610, 1977

171. Kahn CR, Rosen SW, Weintraub BD, et al: Ectopic production of chronic gonadotropin and its subunits by islet-cell tumors—A specific marker for malignancy. N Engl J Med 297:565-569, 1977

172. Vaitukaitis JL: When is a tumor marker not a tumor marker? (Editorial). N Engl J Med 293:1370-1371, 1976

173. Rutanen EM, Seppala M: The hCG-beta subunit radioimmunoassay in nontrophoblastic gynecologic tumors. Cancer 41:692-696, 1978

174. Kurman RJ, Scardino PT, McIntyre KR, et al: Cellular localization of alpha-fetoprotein and human chorionic gonadotropin in germ cell tumors of the testis using an indirect immunoperoxidase technique—A new approach to classification utilizing tumor markers. Cancer 40:2136-2151, 1977

175. Sherbert GV: Epigenetic mechanisms and paraneoplastic phenomena. Ann NY Acad Sci 230:516-532, 1974

176. Richardson RL, Greco FA, Oldham RK, et al: Tumor products and potential markers in small cell lung cancer. Semin Oncol 5:253-262, 1978

177. Warner TFCS: Cell hybridisation in the genesis of ectopic hormone-secreting tumors. Lancet 1:1259-1260, 1974

178. Acevedo HF, Slifkin M, Pouchet G, et al: Immunohistochemical localization of a choriogonadotropin-like protein in bacteria isolated from cancer patients. Cancer 41:1217-1229, 1978

179. Skrabanek P, Powell D: Unifying concept of non-pituitary ACTH-secreting tumors: Evidence of common origin of neural-crest tumors, carcinoids, and oat-cell carcinoma. Cancer 42:1263-1269, 1978

180. Tischler AS: Small cell carcinoma of the lung: Cellular origin and relationship to other neoplasms. Semin Oncol 5:244-252, 1978

181. Godwin JD, Brown CC: Comparative epidemiology of carcinoid and oat-cell tumors of the lung. Cancer 40:1671-1673, 1977

182. Forbes JT, Greco FA, Oldham RK: Immunologic aspects of small cell carcinoma. Semin Oncol 5:263-271, 1978

183. Hall TC: Oncocognitive autoimmunity and other paraneoplastic syndromes yet to be described. Ann NY Acad Sci 230:565-570, 1974

184. Nathanson L, Hall TC: Lung tumors: How they produce their syndromes. Ann NY Acad Sci 230:367-377, 1974

185. Monaco ME, Bronzert DA, Tormey DC, et al: Casein production by human breast cancer. Cancer Res 37:749-754, 1977

186. Rosen SW, Weintraub BD, Vaitukaitis JL, et al: Placental proteins and their subunits as tumor markers. Ann Intern Med 82:71-83, 1975

187. Tashjian AH Jr, Weintraub BC, Barowsky NJ, et al: Subunits of human chorionic gonadotropin: Unbalanced synthesis and secretion by clonal cell strains derived from a bronchogenic carcinoma. Proc Natl Acad Sci USA 70:1419-1422, 1973

188. Unproven Methods of Cancer Management. New York, American Cancer Society, 1971, pp 33-36